REMARKS

Status of the Claims

Claims 1-4 and 6-14 are currently pending. Applicants amend claim 6 to remove the word "model" from the phrase "model compound." The word "model" is not necessary in claim 6 because the claimed compounds are also listed within the body of the claim. Therefore, its removal does not alter the scope or meaning of any claim. Applicants respectfully request the entry of this amendment.

The Claims Are Definite

The Office rejects claims 1-4 and 6-14 under 35 U.S.C. § 112, second paragraph, asserting that certain elements or terms in claims 1 and 6 are indefinite. Applicants traverse this rejection and offer the following comments to assist the Examiner.

Applicants first note that § 112, second paragraph, is satisfied by *reasonable* clarity, not exact precision. M.P.E.P. § 2173.02; emphasis in original. Further, the requirement for definiteness is judged from the point of view of one of ordinary skill in the art. M.P.E.P. § 2171. So long as one of ordinary skill in the art, with the application to provide guidance, would understand the meaning of the terms used, the claims are definite. M.P.E.P. § 2173.02.

The Office first contends that the "tracer" recited in claim 1, part (c) is unclear. Yet, the Office has not considered that "tracer" is a frequently used and well understood term in the art. For example, Iizuka et al. (*Biomedical Res.* 11(6): 417-423 (1990)), which this Office Action cites, comments, in reference to certain radioimmunoassay kits, "[t]hese methods required a long second incubation and separation of bound and free

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tracer . . . by centrifugation at 4 °C." (*Id.* at page 417, 2nd col., emphasis added.) The application at page 21, lines 21-32, shows that a tracer is also used in several inferior, prior art radioimmunoassays.

Applicants also traverse this rejection because the instant "tracer" is described at several places in the application, including a detailed discussion in one of the working examples. Page 5, lines 4-5, and page 11, lines 18-20, describe example tracers according to the instant invention. Page 12, beginning at line 16, describes an example of how to make such tracers and tag them with a chemiluminescent label so that they can be monitored in the claimed assay. Page 13, line 25 to page 14, line 12, provides an example of how to perform an assay according to the instant invention. As to the function of the tracer, Figures 3, 8, and 9, and several working examples illustrate its use according to this assay, as discussed below. For all of the above reasons, claim 1, part (c) is clear.

The Office next contends that claim 1, part (e) is indefinite. An example of such a "C-peptide second antibody bead" is described at several places in the application, for example, at page 5, line 10: "Polystyrol beads coated with secondary antibodies . . . to capture goat antiinsulin C-peptide antibodies with our without bound antigens or tracer." Applicants submit that the purpose and identity of part (e) is clear from this description.

The Office also asserts that the relationship between claim 1, part (f) and its preceding parts is unclear. However, the working examples in the application and their accompanying figures provide numerous examples of how the impurities are detected according to the claimed method. These descriptions are more than adequate for those of ordinary skill in the art to understand the claimed detection process. For instance,

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Example I, part III, at page 15 of the specification, describes the determination of the presence of an impurity according to the instant claims by monitoring the ability of a C-peptide impurity of part (a) to compete with the tracer of part (c) for binding to the antibody of part (d). One of ordinary skill in the art would understand that the labeled "C-peptide second antibody bead" of part (e) is used, for example, to separate the tracer bound to the antibody of part (d), whose label is monitored, from any free tracer that has been competed off the antibody by the C-peptide impurity of part (a). Thus, there is no need to amend claim 1, as those of ordinary skill in the art would understand the meaning of the terms therein and the relationships between the steps or elements.

Finally, the Office rejects claim 6, asserting that the term "model compounds" is unclear. This rejection is moot as Applicants have removed the term "model" from claim 6, solely to speed prosecution. In any event, the word "model" does not affect the scope or meaning of claim 6 because the claimed compounds are specifically listed within the body of the claim. Applicants also note that the specification makes the meaning of "model compounds" clear. For example, they are described at page 2, line 31, to page 3, line 4, and examples are depicted in Figure 1, and at page 20, lines 1-23. Thus, the meaning of "model compounds" in claim 6 is definite.

Applicants respectfully request the withdrawal of these rejections in light of these remarks.

Claims 1-3, 6-12 and 14 Are Nonobvious

The Office rejects claims 1-3, 6-12 and 14 under 35 U.S.C. § 103(a) over Iizuka et al. ("Iizuka"; *Biomedical Res.*, 11(6): 417-423 (1990)), in view of Hara et al. ("Hara"; EP 0 484 961 A1) and Newgard (U.S. Patent No. 5,811,266). (Office Action at pages 3-

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5.) According to the Office, Iizuka presents the same process steps as claim 1. The Office acknowledges that Iizuka's assay has three key deficiencies. First, it is performed on a natural insulin sample rather than a recombinantly produced insulin sample. Second, Iizuka's assay uses radioactive ^{125}I detection rather than non-radioactive detection. Third, Iizuka does not use a second antibody with "at least one label." (Office Action at page 4.) The Office relies on Hara and Newgard to provide the missing elements of Iizuka. The Office contends that Hara suggests non-radioactive detection and labeling a second antibody while Newgard suggests screening of recombinant insulin samples. (*Id.*) Applicants respectfully traverse this rejection.

The first of the three requirements for a *prima facie* case of obviousness is a motivation or suggestion to combine the teachings of the references so as to produce the claimed invention. M.P.E.P. §§ 2143 and 2143.01. That motivation to combine references must come from the references themselves or from the knowledge generally available to one of ordinary skill in the art; not from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. Further, the mere fact that the references ***can*** be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The modification or combination must be ***desirable***, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000).

In addition, the Office bears the burden to support its conclusions with substantial evidence or scientific reasoning firmly grounded in fact. *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Conclusory statements are insufficient to support a *prima facie* case. *Lee*, 61 U.S.P.Q.2d 1430.

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Finally, all of the teachings of the references must be considered in the obviousness inquiry. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). One cannot pick and choose only those elements of a reference that support a rejection while omitting other elements that do not support the rejection. *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

The Office's reasoning for combining Iizuka with Hara and Newgard does not satisfy these requirements because the Office does not explain how one of ordinary skill in the art would desire to alter Iizuka's assay to omit radioactivity, label the second antibody, and detect C-peptide impurities in a recombinant sample.

Iizuka discusses a radioimmunoassay and is satisfied with using ^{125}I radioactive tracers in that assay. Iizuka does not suggest, either expressly or implicitly, that any other, non-radioactive methods would be preferable. In addition, the Office does not contend that Iizuka, or the other cited publications, point out any potential problems with radioimmunoassays.

Newgard does not appear to even mention an impurity-detection process. Thus, its teachings are of little relevance beyond the general notion that insulin can be made recombinantly.

Hara does not suggest any reason to use a non-radioactive label over a radioactive one. For example, Hara states that the "labeling substance that can be used in the present invention is not particularly limited," then goes on to include several known methods of labeling as possibilities, including three different radioactive isotopes, several enzymatic labels, and several different fluorescent labels, without suggesting that there should be any preference among them. (See Hara at page 2, lines 50-54.)

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Further, Hara's published claims 3 and 7 recite all three types of labeling - radioactive, fluorescent, and enzymatic. Thus, Hara does not point one of ordinary skill in the art away from radioactivity.

Hara also does not motivate one of ordinary skill in the art to label *both* an antibody and a tracer as Applicants do. Instead, when Hara labels an antibody, it doesn't use any tracer. (Hara at page 2, lines 35-50, describing its "sandwich assay.") When Hara labels a tracer, it doesn't use any second antibody. (Hara at page 3, line 10-29, describing its "competitive assay.") Thus, Hara does not suggest altering Iizuka to include *both* a labeled tracer and a labeled second antibody bead as Applicants do. At best, Hara suggests that one component of a detection assay should have a label, and that the label could, in principle, be radioactive as well as non-radioactive. (See Applicants' remarks filed April 21, 2003, at pages 11-12 for further discussion of Hara.)

Iizuka and Hara's teachings conflict in other ways as well. Iizuka suggests a bead-based assay, while Hara teaches a microtiter-plate assay. Thus, even if, *arguendo*, Hara did suggest altering Iizuka to use a non-radioactive label, it would just as strongly suggest altering Iizuka to replace the second-antibody beads with a microtiter-plate system. Indeed, this shows that the Office has not considered Hara and Iizuka's teachings as a whole, but has instead impermissibly chosen only the elements of the two publications that support this rejection. The teachings of Iizuka and Hara as a whole do not point those in the art toward a combination of non-radioactive labels and second-antibody beads over radioactive labels and microtiter plates.

To illustrate these points, Applicants direct the Office's attention to an analogous case from the Federal Circuit, *Winner v. Wang*, 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000).

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The Federal Circuit in *Winner* considered whether patent claims directed to an automobile anti-theft device were obvious in light of four prior art references. *Id.* at 1582-3 and 1586-7. The claimed device uses a ratcheting mechanism to lock onto a car's steering wheel. One prior art reference disclosed a similar steering wheel locking device (a.k.a. "The Club") that locks onto the steering wheel by a dead-bolt mechanism instead of by a ratcheting mechanism. Another reference disclosed a different type of steering wheel locking device that uses a ratcheting mechanism. *Id.* at 1583. The Federal Circuit concluded that the claims were not obvious because nothing in any of the cited references suggested that any problem would be overcome in replacing a dead-bolt mechanism with a ratcheting mechanism. 53 U.S.P.Q.2d at 1587. In other words, "there was no apparent disadvantage to the dead-bolt mechanism." *Id.* Thus, the combination of references would, at best, produce a feasible result, but not a desirable result. *Id.*

Winner illustrates that motivation to combine is found when the prior art references create a *desire* in the person of ordinary skill in the art to follow the applicant's particular path, not when the references merely indicate that the path is one of several feasible possibilities. Like the references in *Winner*, Iizuka, Hara, and Newgard do not suggest that those in the art should follow any particular path. At best, they merely illustrate that several kinds of labels and antibody substrates could be useful in principle.

Even if, *arguendo*, the Office had raised a *prima facie* case, Applicants' data also demonstrate that the claimed assay is unexpectedly superior to assays such as Iizuka's and Hara's. For example, Applicants compared their assay to three commercial

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radioimmunoassays like Iizuka's, intended for detection of C-peptides – the RIA-coat C-peptide, Human C-peptide RIA Kit, and Human Proinsulin RIA Kit. (See the specification at pages 6-7 and pages 21-28, Example II; see also page 1, third full paragraph for a discussion of general disadvantages of radioimmunoassays.) The instant, claimed assay was superior to each one. The first assay was not able to distinguish C-peptide impurities in a high insulin background. (*Id.* at pages 6-7.) The second was only useful in a limited pH range. (*Id.*) The third was unable to detect monkey C-peptide impurities, which greatly limits its usefulness in assaying recombinant insulin samples, as recombinant insulins normally use a monkey C-peptide rather than a human one. (*Id.*)

The claimed assay is also superior to a sandwich ELIZA assay similar to Hara's assays. (Specification at pages 22-28, Example II.) That ELIZA assay generally gave variable, unsatisfactory results compared to the claimed assay. (Specification at page 27, lines 8-18.) Further, that ELIZA assay was designed to detect only isolated C-peptide. Thus it is not clear if its antibodies could recognize other C-peptide impurities such as preproinsulin. (*Id.*)

Finally, the Office contends that some of the dependent claims are also obvious in light of these three publications. In particular, the Office asserts that claim 10 is obvious in light of the publications because it represents only the optimization of a variable or range. (Office Action at page 4, final paragraph.) However, claim 10 recites a particular requirement of the antibody (the ability to detect a C-peptide impurity in a background of 1 mg/mL human insulin) rather than a simple change of temperature or concentration.

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The Office bears the burden to support this rejection with more than such conclusory statements. *See In re Lee*, 61 U.S.P.Q.2d 1430. For example, the Office has not explained how Iizuka's or Hara's teachings show that the antibodies they use are able to discriminate between human insulin and C-peptide according to this claim. Further, Applicants specifically tested their claimed assay system against three prior radioimmunoassay systems like Iizuka's and found that at least one of these prior systems is incapable of distinguishing C-peptide impurities in a background of 1 mg/mL human insulin, as claim 10 requires. (See the specification at page 6, line 7, to page 7, line 9.) In contrast, Applicants' Example I, Part III, at pages 14 and 15 demonstrates that the instant claimed assay can distinguish C-peptide impurities in a background of 1 mg/mL human insulin.

For all of these reasons, Applicants submit that the instant claims are nonobvious and request the withdrawal of this rejection.

Claims 4 and 13 Are Nonobvious

The Office further rejects claims 4 and 13 under 35 U.S.C. § 103(a) over the above cited art in combination with Naithani et al. (Abstract from *Fed. Rep. Ger. Intl. Congress Ser.* 468: 94-98 (1979)). (Office Action at page 5.) The Office relies on Naithani et al. for a discussion of an anti-monkey C-peptide antibody. (*Id.*) Applicants traverse this rejection for the same reasons Applicants traverse the rejection to claims 1-3, 6-12, and 14 above. Because there is no motivation to combine Iizuka with Hara and Newgard, claims 4 and 13 must also be nonobvious. Hence, Applicants also request the withdrawal of this rejection.

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CONCLUSION

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees not found herewith to Deposit Account No. 06-0916.

Respectfully submitted,

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